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(54) Title: N"-Substituted 9a-N-(N'-carbamoyl-γ-aminopropyl), 9a-N-(N' -thiocarbamoyl-γ-aminopropyl), 9a-N-[N'-(β-cyanoethyl)-N'-carbamoyl-γ-aminopropyl] and 9a-N-[N'-(β-cyanoethyl)-N'-thiocarbamoyl-γ-aminopropyl] derivatives of 9-de

(57) Abstract: The invention relates to N"-substituted 9a-N-(N'-carbamoyl-γ-aminopropyl), 9a-N-(N'-thiocarbamoyl-γ-aminopropyl), 9a-N-[N'-(β-cyanoethyl)-N'-carbamoyl-γ-aminopropyl] and 9a-N-[N'-(β-cyanoethyl)-N'-thiocarbamoyl-γ-aminopropyl] derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A, novel semisynthetic macrolide antibiotics of the azalide series, of the general formula 1, wherein R represents H or cladinosyl moiety, R<sup>1</sup> represents H or (β-cyanoethyl moiety, R<sup>2</sup> represents isopropyl, 1-naphtyl, 2-naphtyl, benzyl, 2-(trifluoromethyl)phenyl, 3-phenylpropyl, β-phenylethyl, ethoxycarbonylmethyl, 1-(1-naphtyl)ethyl, 3,4,5-trimethoxyphenyl and 2,4-dichlorophenyl group, and X represents O and S, and their acceptable addition salts thereof with inorganic or organic acids, to the process for preparation of their pharmaceutical compositions as well as the use their compositions in the treatment of bacterial infections.

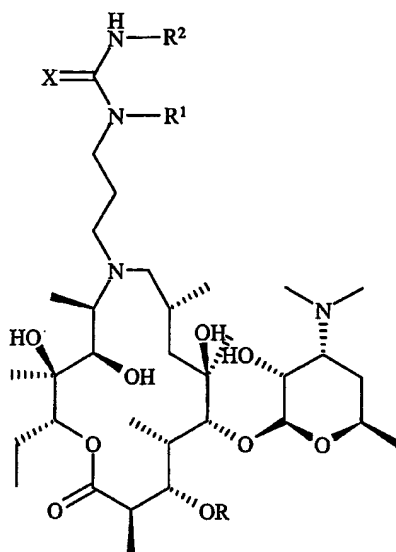
**N''-Substituted 9a-N-(N'-carbamoyl- $\gamma$ -aminopropyl), 9a-N-(N'-thiocarbamoyl- $\gamma$ -aminopropyl), 9a-N-[N'-( $\beta$ -cyanoethyl)-N'-carbamoyl- $\gamma$ -aminopropyl] and 9a-N-[N'-( $\beta$ -cyanoethyl)-N'-thiocarbamoyl- $\gamma$ -aminopropyl] derivatives of 9-deoxo-9-dihydro-9a-  
9a-  
-aza-9a-homoerithromycin A and 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A**

**Technical field**

Int. Cl. C 07H 17/08, A61K 31/71

**Technical Problem**

The present invention relates to N''-substituted 9a-N-(N'-carbamoyl- $\gamma$ -aminopropyl), 9a-N-(N'-thiocarbamoyl- $\gamma$ -aminopropyl), 9a-N-[N'-( $\beta$ -cyanoethyl)-N'-carbamoyl- $\gamma$ -aminopropyl] and 9a-N-[N'-( $\beta$ -cyanoethyl)-N'-thiocarbamoyl- $\gamma$ -aminopropyl] derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A, novel semisynthetic macrolide antibiotics of the azalide series having antibacterial activity, of the general formula 1,



1

wherein R represents H or cladineryl moiety, and  $R^1$  represents H or  $\beta$ -cyanoethyl group,  $R^2$  represents isopropyl, 1-naphthyl, 2-naphthyl, benzyl, 2-(trifluoromethyl)phenyl, 3-phenylpropyl,  $\beta$ -phenylethyl, ethoxycarbonylmethyl, 1-(1-naphthyl)ethyl, 3,4,5-trimethoxyphenyl and 2,4-dichlorophenyl group, and X represents O or S, to pharmaceutically acceptable addition salts thereof with inorganic or organic acids, to a process for the preparation of the pharmaceutical compositions as well as to the use of the pharmaceutical compositions obtained in the treatment of bacterial infections.

### Prior Art

Erithromycin A is a macrolide antibiotic, whose structure is characterized by 14-membered macrolactone ring having carbonyl group in C-9 position. It was found by McGuire in 1952 [*Antibiot. Chemother.*, 2 (1952) 281] and for over 40 years it has been considered as a reliable and effective antimicrobial agent in the treatment of diseases caused by Gram-positive and some Gram-negative microorganisms. However, in an acidic medium it is easily converted into anhydroerythromycin A, an inactive C-6/C-12 metabolite of a spiroketal structure [P. Kurath et al.,

*Experientia* 27 (1971) 362]. It is well-known that spirocyclisation of aglycone ring of erythromycin A is successfully inhibited by a chemical transformation of C-9 ketones or hydroxy groups in C-6 and/or C-12 position. By the oximation of C-9 ketones [S. Đokić et al., *Tetrahedron Lett.* 1967: 1945] and by subsequently modifying the obtained 9(E)-oxime into 9-[O-(2-methoxyethoxy)methyloxime]erythromycin A (ROXITHROMYCIN) [G. S. Ambrieres, Fr. pat. 2,473,525, 1981] or 9(S)-erythromycylamine [R. S. Egan et al., *J. Org. Chem.* 39 (1974) 2492] or a more complex oxazine derivative thereof, 9-deoxo-11-deoxy-9,11-{imino[2-(2-methoxyethoxyethylidene)oxy]}-9(S)-erythromycin A (DIRITHROMYCIN) [P. Lugar et al., *J. Crist. Mol. Struct.* 9 (1979) 329], novel semisynthetic macrolides were synthesized, whose basic characteristic, in addition to a greater stability in an acidic medium, is a better pharmacokinetics and a long half-time with regard to the parent antibiotic erythromycin A. In a third way for modifying C-9 ketones use is made of Beckmann rearrangement of 9(E)-oxime and of a reduction of the obtained imino ether (G. Kobrehel et al., U.S. Pat. 4,328,334, 1982.) into 11-aza-10-deoxo-10-dihydroerythromycin A (9-deoxo-9a-aza-9a-homoerythromycin A) under broadening the 14-member ketolactone ring into a 15-member azalactone ring. By reductive N-methylation of 9a-amino group according to Eschweiler-Clark process (G. Kobrehel et al., BE Pat. 892,397, 1982.) or by a preliminary protection of amino group by means of conversion into the corresponding N-oxides and then by alkylation and reduction [G. M. Bright, U.S. Pat., 4,474,768, 1984.] N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A (9-deoxo-9a-methyl-9a-aza-9a-homoerythromycin A, AZITHROMYCIN) was synthesized, a prototype of azalide antibiotics, which, in addition to a broad antimicrobial spectrum including Gram-negative bacteria and intracellular microorganisms, are characterized by a specific mechanism of transport to the application site, a long biological half-time and a short therapy period. In EP A 0316128 (Bright G. M. et al.) novel 9a-allyl and 9a-propargyl derivatives of 9-deoxo-9a-aza-9a-homoerythromycin A are disclosed and in U.S. Pat. 4,492,688, from 1985 (Bright G. M.) the synthesis and the antibacterial activity of the corresponding cyclic ethers are disclosed. In the there are further disclosed the synthesis and the activity spectrum of novel 9-deoxo-9a-aza-11-deoxy-9a-

-homoerythromycin A 9a,11-cyclic carbamates and O-methyl derivatives thereof (G. Kobrehel et al., *J. Antibiot.* **46** (1993) 1239-1245).

By reaction of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A with isocyanates or isothiocyanates respectively [N. Kujundžić et al. Croat. Pat. 931480, 1993.], 9a-N-(N'-carbamoyl) and 9a-N-(N'-thiocarbamoyl) derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A with a certain antibacterial activity are obtained.

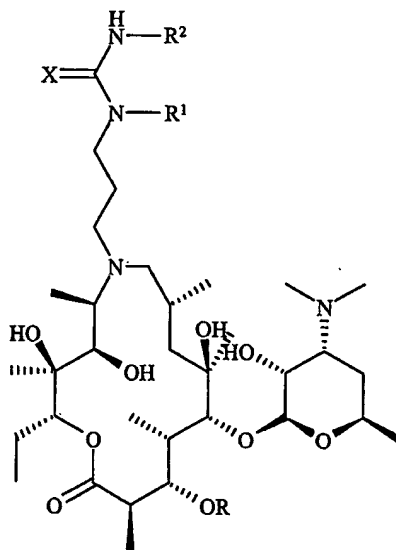
According to the known and established Prior Art, N''-substituted 9a-N-(N'-carbamoyl- $\gamma$ -aminopropyl), 9a-N-(N'-thiocarbamoyl- $\gamma$ -aminopropyl), 9a-N-[N'-( $\beta$ -cyanoethyl)-N'-carbamoyl- $\gamma$ -aminopropyl] and 9a-N-[N'-( $\beta$ -cyanoethyl)-N'-thiocarbamoyl- $\gamma$ -aminopropyl] derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A and pharmaceutically acceptable addition salts thereof with inorganic or organic acids, a process for the preparation thereof as well as the preparation methods and use in pharmaceutical preparations have not been disclosed as yet.

It has been found and it is object of the present invention, that N''-substituted 9a-N-(N'-carbamoyl- $\gamma$ -aminopropyl), 9a-N-(N'-thiocarbamoyl- $\gamma$ -aminopropyl), 9a-N-[N'-( $\beta$ -cyanoethyl)-N'-carbamoyl- $\gamma$ -aminopropyl] and 9a-N-[N'-( $\beta$ -cyanoethyl)-N'-thiocarbamoyl- $\gamma$ -aminopropyl] derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A, novel semisynthetic macrolide antibiotic of the azalide series and pharmaceutically acceptable addition salts thereof with inorganic or organic acids, may be prepared by reacting 9a-N-( $\gamma$ -aminopropyl) and 9a-N-[N'-( $\beta$ -cyanoethyl)- $\gamma$ -aminopropyl] derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A with isocyanates or isothiocyanates and optionally by reacting the obtained N''-substituted 9a-N-(N'-carbamoyl- $\gamma$ -aminopropyl), 9a-N-(N'-thiocarbamoyl- $\gamma$ -aminopropyl), 9a-N-[N'-( $\beta$ -cyanoethyl)-N'-carbamoyl- $\gamma$ -aminopropyl] and 9a-N-[N'-( $\beta$ -cyanoethyl)-N'-thiocarbamoyl- $\gamma$ -aminopropyl]

derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A with organic and inorganic acids.

### Technical Solution

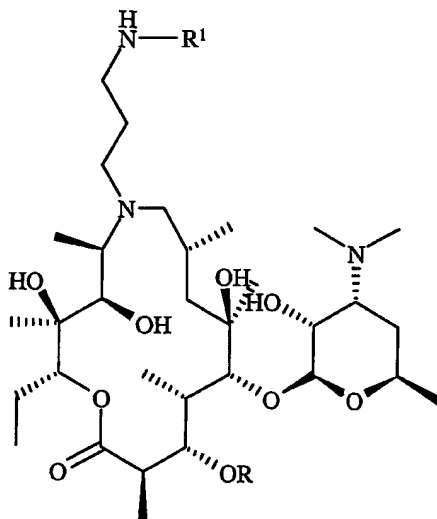
It has been found that novel N"-substituted 9a-N-(N'-carbamoyl- $\gamma$ -aminopropyl), 9a-N-(N'-thiocarbamoyl- $\gamma$ -aminopropyl), 9a-N-[N'-( $\beta$ -cyanoethyl)-N'-carbamoyl- $\gamma$ -aminopropyl] and 9a-N-[N'-( $\beta$ -cyanoethyl)-N'-thiocarbamoyl- $\gamma$ -aminopropyl] derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A of the general formula 1,



1

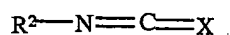
wherein R represents H or cladinosyl group, R<sup>1</sup> represents H or  $\beta$ -cyanoethyl moiety, R<sup>2</sup> represents isopropyl, 1-naphtyl, 2-naphtyl, benzyl, 2-(trifluoromethyl)phenyl, 3-phenylpropyl,  $\beta$ -phenylethyl, ethoxycarbonylmethyl, 1-(1-naphtyl)ethyl, 3,4,5-trimethoxyphenyl and 2,4-dichlorophenyl group, and X represents O or S, and their acceptable addition salts there of with inorganic or organic acids, may be prepared by reacting 9a-N-( $\gamma$ -aminopropyl) and 9a-N-[N'-( $\beta$ -cyanoethyl)- $\gamma$ -aminopropyl] derivatives of 9-deoxo-9-dihydro-9a-aza-9a-

-homoeithromycin A and 5-O-desosaminy-9-deoxo-9-dihydro-9a-aza-9a-homoeithronolide A general formula 2,



2

wherein R represents H or cladinosyl group and R<sup>1</sup> represents H or β-cyanoethyl moiety, with isocyanates or thioisocyanates general formula 3,



3

wherein R<sup>2</sup> and X have above meanings, in toluene, xylene or some other aprotic solvent, at a temperature 0° to 110°C.

Pharmaceutically acceptable acid addition salts, which also represent an object of present invention, were obtained by reaction N"-substituted 9a-N-(N'-carbamoyl-γ-aminopropyl), 9a-N-(N'-thiocarbamoyl-γ-aminopropyl), 9a-N-[N'-(β-cyanoethyl)-N'-carbamoyl-γ-aminopropyl] and 9a-N-[N'-(β-cyanoethyl)-N'-thiocarbamoyl-γ-aminopropyl] derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoeithromycin A and 5-O-desosaminy-9-deoxo-9-dihydro-9a-aza-9a-homoeithronolide A with an at least equimolar amount of the corresponding inorganic or organic acid such as hydrochloric acid, hydroiodic acid, sulfuric acid, phosphoric acid, acetic acid,

trifluoroacetic acid, propionic acid, benzoic acid, benzenesulfonic acid, methane sulfonic acid, laurylsulfonic acid, stearic acid, palmitic acid, succinic acid, ethylsuccinic acid, lactobionic acid, oxalic acid, salicylic acid and similar acid, in a solvent inert to the reaction. Addition salts are isolated by evaporating the solvent or, alternatively, by filtration after a spontaneous precipitation or a precipitation by the addition of a non-polar cosolvent.

N"-Substituted 9a-N-(N'-carbamoyl- $\gamma$ -aminopropyl), 9a-N-(N'-thiocarbamoyl- $\gamma$ -aminopropyl), 9a-N-[N'-( $\beta$ -cyanoethyl)-N'-carbamoyl- $\gamma$ -aminopropyl] and 9a-N-[N'-( $\beta$ -cyanoethyl)-N'-thiocarbamoyl- $\gamma$ -aminopropyl] derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminy-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A of the general formula 1 and pharmaceutically acceptable addition salts with inorganic or organic acids thereof possess an antibacterial activity *in vitro*.

Minimal inhibitory concentration (MIC) is defined as the concentration which shows 90% growth inhibition, and was determined by broth dilution methods National Committee for Clinical Laboratory Standards (NCCLS, M7-A2 protocols). Final concentration of test substances were in range from 64 to 0.125 mg/l. MIC levels for all compound were determined on panel of susceptible and resistant Gram positive bacterial strains (*S. aureus*, *S. pneumoniae* and *S. pyogenes*) and on Gram negative strains (*E. coli*, *H. influenzae*, *E. faecalis*, *M. catarrhalis*).

It is evident from Table 1 and Table 2 that standard strains are susceptible to newly synthesized compounds of general formula 1. Thus they may be used as therapeutic agents in the treatment of infective diseases in animals, especially mammals and humans, caused by a broad spectrum of Gram-positive and Gram-negative bacteria, mycoplasmas and generally pathogenic microorganisms that are susceptible to the compounds of the formula 1. To this purpose the above compounds and pharmaceutically acceptable acid addition salts thereof may be administered orally in usual doses from 0.2 mg/kg body weight daily to about 250 mg/kg/day, most



preferably from 0.5-50 mg/kg/day, or parenterally in the form of subcutaneous and intramuscular injections.

Process for the preparation of N"-substituted 9a-N-(N'-carbamoyl- $\gamma$ -aminopropyl), 9a-N-(N'-thiocarbamoyl- $\gamma$ -aminopropyl), 9a-N-[N'-( $\beta$ -cyanoethyl)-N'-carbamoyl- $\gamma$ -aminopropyl] and 9a-N-[N'-( $\beta$ -cyanoethyl)-N'-thiocarbamoyl- $\gamma$ -aminopropyl] derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminy-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A of this invention is illustrated by the following Examples which should in no way be construed as a limitation of the scope thereof.

TABLE 1. Antibacterial *in vitro* activity of novel N"-substituted 9a-N-(N'-carbamoyl- $\gamma$ -aminopropyl) and 9a-N-(N'-thiocarbamoyl- $\gamma$ -aminopropyl) derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A presented as MIC values in comperison with erythromycin A (Er).

Test organisms	MIK $\mu$ g/ml												
Compound from example	1	2	3	4	5	6	7	8	9	10	11	12*	Er
<i>S. aureus</i> ATCC 13709	2	0.5	0.5	2	2	2	1	1	8	16	4	8	$\leq 0.125$
<i>S. pneumoniae</i>	$\leq 0.125$	$\leq 0.125$	$\leq 0.125$	$\leq 0.125$	$\leq 0.125$	$\leq 0.125$	$\leq 0.125$	$\leq 0.125$	$\leq 0.125$	8	$\leq 0.125$	16	$\leq 0.125$
<i>S. pyogenes</i>	$\leq 0.125$	$\leq 0.125$	$\leq 0.125$	$\leq 0.125$	$\leq 0.125$	$\leq 0.125$	$\leq 0.125$	$\leq 0.125$	$\leq 0.125$	$\leq 0.125$	$\leq 0.125$	$\leq 0.125$	0.25
<i>S. pyogenes</i> iMLS	8	2	4	2	4	8	4	4	16	8	32	2	$> 64$
<i>S. pyogenes</i> M	32	4	8	4	4	32	8	8	64	16	64	8	8
<i>M. catarrhalis</i> ATCC 23246	0.5	0.25	1	1	2	8	1	1	4	4	16	0.5	-
<i>H. influenzae</i> ATCC 49247	32	1	2	2	2	16	2	2	32	2	16	2	2
<i>E. faecalis</i> ATCC 29212	32	4	16	8	4	64	16	16	$> 64$	16	$> 64$	8	1
<i>E. coli</i> ATCC 25922	16	8	16	16	8	32	16	32	$> 64$	64	$> 64$	32	32

TABLE 2. Antibacterial *in vitro* activity of novel N"-substituted 9a-N-[N'-( $\beta$ -cyanoethyl)-N'-carbamoyl- $\gamma$ -aminopropyl] and 9a-N-[N'-( $\beta$ -cyanoethyl)-N'-thiocarbamoyl- $\gamma$ -aminopropyl] derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A presented as MIC values in comperison with erythromycin A (Er).

Test organisms	MIK $\mu$ g/ml												
Compound from example	27	28	29	30	31	32	33	34	36	37	38	39*	Er
<i>S. aureu</i> ATCC 13709	4	1	2	1	4	4	1	1	2	4	1	1	$\leq 0.125$

<i>S. pneumoniae</i> ATCC	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125
<i>S. pyogenes</i> ATCC	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	0.25
<i>S. pyogenes</i> iMLS	8	2	16	2	4	8	4	4	8	47	2	32	>64
<i>S. pyogenes</i> M	32	4	64	4	4	32	8	8	16	8	8	64	8
<i>M. catarrhalis</i> ATCC 23246	0.5	0.25	4	1	2	8	1	1	4	1	0.5	16	-
<i>H. influenzae</i> ATCC 49247	32	1	32	2	2	16	2	2	2	2	2	16	2
<i>E. faecalis</i> ATCC 29212	32	4	>64	8	4	64	16	16	16	16	8	>64	1
<i>E. coli</i> ATCC 25922	16	8	>64	16	8	32	16	32	64	16	32	>64	32

**Example 1****9-Deoxo-9-dihydro-9a-N-(N'-isopropylcarbamoyl- $\gamma$ -aminopropyl)-9a-aza-9a-homoerithromycin A**

A mixture of 1.0 g (1.26 mmol) 9-deoxo-9-dihydro-9a-aza-9a-( $\gamma$ -aminopropyl)-9a-homoerithromycin A and 0.1 g (1.3 mmol) of isopropylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-(N'-isopropylcarbamoyl- $\gamma$ -aminopropyl)-9a-aza-9a-homoerithromycin A was obtained.

MS(ES<sup>+</sup>)m/z = 877.

**Example 2****9-Deoxo-9-dihydro-9a-N-[N'-(1-naphtyl)carbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A**

A mixture of 1.0 g (1.26 mmol) 9-deoxo-9-dihydro-9a-aza-9a-( $\gamma$ -aminopropyl)-9a-homoerithromycin A and 0.22 g (1.26 mmol) of 1-naphtylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-(1-naphtyl)carbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES<sup>+</sup>)m/z = 961.

**Example 3****9-Deoxo-9-dihydro-9a-N-(N'-benzylcarbamoyl- $\gamma$ -aminopropyl)-9a-aza-9a-homoerithromycin A**

A mixture of 1.0 g (1.26 mmol) 9-deoxo-9-dihydro-9a-aza-9a-( $\gamma$ -aminopropyl)-9a-homoerithromycin A and 0.17 g (1.3 mmol) of benzylisocyanate in 10 ml dry

toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-(N'-benzylcarbamoyl- $\gamma$ -aminopropyl)-9a-aza-9a-homoerithromycin A was obtained.

MS(ES<sup>+</sup>)m/z = 925.

#### Example 4

##### **9-Deoxo-9-dihydro-9a-N-(N'-benzylthiocarbamoyl- $\gamma$ -aminopropyl)-9a-aza-9a-homoerithromycin A**

A mixture of 1.0 g (1.26 mmol) 9-deoxo-9-dihydro-9a-aza-9a-( $\gamma$ -aminopropyl)-9a-homoerithromycin A and 0.17 g (1.3 mmol) of benzyliothiocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-(N'-benzylthiocarbamoyl- $\gamma$ -aminopropyl)-9a-aza-9a-homoerithromycin A was obtained.

MS(ES<sup>+</sup>)m/z = 941.

#### Example 5

##### **9-Deoxo-9-dihydro-9a-N-[N'-(1-naphtyl)thiocarbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A**

A mixture of 1.0 g (1.26 mmol) 9-deoxo-9-dihydro-9a-aza-9a-( $\gamma$ -aminopropyl)-9a-homoerithromycin A and 0.17 g (1.3 mmol) of 1-naphtyliothiocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-(1-naphtyl)thiocarbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES<sup>+</sup>)m/z = 977.

**Example 6****9-Deoxo-9-dihydro-9a-N-[N'-(2-trifluoromethyl)phenylcarbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A**

A mixture of 1.0 g (1.26 mmol) 9-deoxo-9-dihydro-9a-aza-9a-( $\gamma$ -aminopropyl)-9a-homoerithromycin A and 0.24 g (1.3 mmol) of 2-(trifluoromethyl)phenylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-(2-trifluoromethylphenyl)carbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES<sup>+</sup>)m/z = 979.

**Example 7****9-Deoxo-9-dihydro-9a-N-[N'-(3-phenylpropyl)thiocarbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A**

A mixture of 1.0 g (1.26 mmol) 9-deoxo-9-dihydro-9a-aza-9a-( $\gamma$ -aminopropyl)-9a-homoerithromycin A and 0.22 g (1.3 mmol) of 3-phenylpropylisothiocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-(3-phenylpropyl)thiocarbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES<sup>+</sup>)m/z = 969.

**Example 8****9-Deoxo-9-dihydro-9a-N-[N'-( $\beta$ -phenylethyl)carbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A**

A mixture of 1.0 g (1.26 mmol) 9-deoxo-9-dihydro-9a-aza-9a-( $\gamma$ -aminopropyl)-9a-homoerithromycin A and 0.21 g (1.3 mmol) of  $\beta$ -phenylethylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -phenylethyl)carbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES<sup>+</sup>)m/z = 979.

#### Example 9

##### **9-Deoxo-9-dihydro-9a-N-(N'-ethoxycarbonylmethylcarbamoyl- $\gamma$ -aminopropyl)-9a-aza-9a-homoerithromycin A**

A mixture of 1.0 g (1.26 mmol) 9-deoxo-9-dihydro-9a-aza-9a-( $\gamma$ -aminopropyl)-9a-homoerithromycin A and 0.16 g (1.3 mmol) of ethoxycarbonylmethylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-(N'-ethoxycarbonylmethylcarbamoyl- $\gamma$ -aminopropyl)-9a-aza-9a-homoerithromycin A was obtained.

MS(ES<sup>+</sup>)m/z = 921.

#### Example 10

##### **9-Deoxo-9-dihydro-9a-N-{N'-[1-(1-naphtyl)ethylcarbamoyl- $\gamma$ -aminopropyl]}-9a-aza-9a-homoerithromycin A**

A mixture of 1.0 g (1.26 mmol) 9-deoxo-9-dihydro-9a-aza-9a-( $\gamma$ -aminopropyl)-9a-homoerithromycin A and 0.25 g (1.3 mmol) of 1-(1-naphtyl)ethylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on

silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-[1-(1-naphtyl)ethyl carbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES<sup>+</sup>)m/z = 989.

#### Example 11

##### **9-Deoxo-9-dihydro-9a-N-[N'-(3,4,5-trimethoxyphenyl)carbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A**

A mixture of 1.0 g (1.26 mmol) 9-deoxo-9-dihydro-9a-aza-9a-( $\gamma$ -aminopropyl)-9a-homoerithromycin A and 0.26 g (1.3 mmol) of 3,4,5-trimethoxyphenylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-(3,4,5-trimethoxyphenyl)carbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES<sup>+</sup>)m/z = 1001.

#### Example 12

##### **9-Deoxo-9-dihydro-9a-N-[N'-(2-naphtyl)carbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A**

A mixture of 1.0 g (1.26 mmol) 9-deoxo-9-dihydro-9a-aza-9a-( $\gamma$ -aminopropyl)-9a-homoerithromycin A and 0.23 g (1.3 mmol) of 2-naphtylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 :



: 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-(2-naphtyl)carbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.  
MS(ES<sup>+</sup>)<sub>m/z</sub> = 961.

### Example 13

#### 9-Deoxo-9-dihydro-9a-N-[N'-(2,4-dichlorophenyl)carbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A

A mixture of 1.0 g (1.26 mmol) 9-deoxo-9-dihydro-9a-aza-9a-( $\gamma$ -aminopropyl)-9a-homoerithromycin A and 0.23 g (1.3 mmol) of 2,4-dichlorophenylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-(2,4-dichlorophenyl)carbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.  
MS(ES<sup>+</sup>)<sub>m/z</sub> = 979.

### Example 14

#### 5-O-Desosaminy-9-deoxo-9-dihydro-9a-N-(N'-isopropylcarbamoyl- $\gamma$ -aminopropyl)-9a-aza-9a-homoerithronolide A

A mixture of 1.0 g (1.57 mmol) 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-( $\gamma$ -aminopropyl)-9a-aza-homoerithronolide A and 0.13 g (1.57 mmol) of isopropylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-(N'-isopropylcarbamoyl- $\gamma$ -aminopropyl)-9a-aza-9a-homoerithronolide A was obtained.  
MS(ES<sup>+</sup>)<sub>m/z</sub> = 719.

**Example 15****5-O-Desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(1-naphtyl)carbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithronolide A**

A mixture of 1.0 g (1.57 mmol) 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-( $\gamma$ -aminopropyl)-9a-aza-homoerithronolide A and 0.13 g (1.57 mmol) of 1-naphtylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(1-naphtyl)carbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES<sup>+</sup>)m/z = 803.

**Example 16****5-O-Desosaminy-9-deoxo-9-dihydro-9a-N-(N'-benzylcarbamoyl- $\gamma$ -aminopropyl)-9a-aza-9a-homoerithronolide A**

A mixture of 1.0 g (1.57 mmol) 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-( $\gamma$ -aminopropyl)-9a-aza-homoerithronolide A and 0.21 g (1.57 mmol) of benzylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-(N'-benzylcarbamoyl- $\gamma$ -aminopropyl)-9a-aza-9a-homoerithronolide A was obtained.

MS(ES<sup>+</sup>)m/z = 767.

**Example 17****5-O-Desosaminy-9-deoxo-9-dihydro-9a-N-(N'-benzylthiocarbamoyl- $\gamma$ -aminopropyl)-9a-aza-9a-homoerithronolide A**

A mixture of 1.0 g (1.57 mmol) 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-( $\gamma$ -aminopropyl)-9a-aza-homoerithronolide A and 0.24 g (1.57 mmol) of benzylisothiocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-(N'-benzylthiocarbamoyl- $\gamma$ -aminopropyl)-9a-aza-9a-homoerithronolide A was obtained.

MS(ES<sup>+</sup>)m/z = 783.

#### Example 18

##### **5-O-Desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(1-naphtyl)thiocarbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithronolide A**

A mixture of 1.0 g (1.57 mmol) 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-( $\gamma$ -aminopropyl)-9a-aza-homoerithronolide A and 0.29 g (1.57 mmol) of 1-naphtylisothiocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(1-naphtyl)thiocarbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES<sup>+</sup>)m/z = 819.

#### Example 19

##### **5-O-Desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(2-(trifluoromethyl)phenylcarbamoyl)- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithronolide A**

A mixture of 1.0 g (1.57 mmol) 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-( $\gamma$ -aminopropyl)-9a-aza-homoerithronolide A and 0.30 g (1.57 mmol) of 2-(trifluoromethyl)phenylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(2-(trifluoromethyl)phenylcarbamoyl)- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES<sup>+</sup>)m/z = 821.

#### Example 20

##### 5-O-Desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(3-phenylpropyl)thiocarbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithronolide A

A mixture of 1.0 g (1.57 mmol) 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-( $\gamma$ -aminopropyl)-9a-aza-homoerithronolide A and 0.28 g (1.57 mmol) of 3-phenylpropylisothiocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(3-phenylpropyl)thiocarbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES<sup>+</sup>)m/z = 811.

#### Example 21

##### 5-O-Desosaminy-9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -phenylethyl)thiocarbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithronolide A

A mixture of 1.0 g (1.57 mmol) 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-( $\gamma$ -aminopropyl)-9a-aza-homoerithronolide A and 0.26 g (1.57 mmol) of  $\beta$ -phenylethylisothiocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered,

wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -phenylethyl)thiocarbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES<sup>+</sup>)m/z = 797.

#### Example 22

##### **5-O-Desosaminyl-9-deoxo-9-dihydro-9a-N-(N'-ethoxykarbonylmethyl-carbamoyl- $\gamma$ -aminopropyl)-9a-aza-9a-homoerithronolide A**

A mixture of 1.0 g (1.57 mmol) 5-O-desosaminyl-9-deoxo-9-dihydro-9a-N-( $\gamma$ -aminopropyl)-9a-aza-homoerithronolide A and 0.20 g (1.57 mmol) of ethoxykarbonylmethylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminyl-9-deoxo-9-dihydro-9a-N-(N'-ethoxykarbonylmethylcarbamoyl- $\gamma$ -aminopropyl)-9a-aza-9a-homoerithronolide A was obtained.

MS(ES<sup>+</sup>)m/z = 763.

#### Example 23

##### **5-O-Desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-(2-naphtyl)carbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithronolide A**

A mixture of 1.0 g (1.57 mmol) 5-O-desosaminyl-9-deoxo-9-dihydro-9a-N-( $\gamma$ -aminopropyl)-9a-aza-homoerithronolide A and 0.27 g (1.57 mmol) of 2-naphtylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-(2-naphtyl)carbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES<sup>+</sup>)m/z = 803.

#### Example 24

##### **5-O-Desosaminy-9-deoxo-9-dihydro-9a-N-[N'-[1-(1-naphthyl)ethyl]carbamoyl-γ-aminopropyl]-9a-aza-9a-homoerithronolide A**

A mixture of 1.0 g (1.57 mmol) 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-(γ-aminopropyl)-9a-aza-homoerithronolide A and 0.31 g (1.57 mmol) of 1-(1-naphthyl)ethylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-[N'-[1-(1-naphthyl)ethyl]carbamoyl-γ-aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES<sup>+</sup>)m/z = 831.

#### Example 25

##### **5-O-Desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(3,4,5-trimethoxyphenyl)-carbamoyl-γ-aminopropyl]-9a-aza-9a-homoerithronolide A**

A mixture of 1.0 g (1.57 mmol) 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-(γ-aminopropyl)-9a-aza-homoerithronolide A and 0.31 g (1.57 mmol) of 3,4,5-trimethoxyphenylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(3,4,5-trimethoxyphenyl)carbamoyl-γ-aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES<sup>+</sup>)m/z = 843.

**Example 26****5-O-Desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(2,4-dichlorophenyl)carbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithronolide A**

A mixture of 1.0 g (1.57 mmol) 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-( $\gamma$ -aminopropyl)-9a-aza-homoerithronolide A and 0.31 g (1.57 mmol) of 2,4-dichlorophenylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(3,4,5-trimethoxyphenyl)carbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES<sup>+</sup>)m/z = 821.

**Example 27****9-Deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)-N'-isopropylcarbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A**

A mixture of 0.5 g (0.591 mmol) 9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A and 0.06 g (0.591 mmol) of isopropylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)-N'-isopropylcarbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES<sup>+</sup>)m/z = 931.

**Example 28****9-Deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)-N'-(1-naphtyl)carbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A**

A mixture of 0.5 g (0.591 mmol) 9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A and 0.11 g (0.591 mmol) of 1-naphtylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)-N'-(1-naphtyl)carbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES<sup>+</sup>)m/z =.

#### Example 29

##### **9-Deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)-N'-benzylcarbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A**

A mixture of 0.5 g (0.591 mmol) 9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A and 0.08 g (0.591 mmol) of benzylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)-N'-benzylcarbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES<sup>+</sup>)m/z = 931.

#### Example 30

##### **9-Deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)-N'-benzylthiocarbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A**

A mixture of 0.5 g (0.591 mmol) 9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A and 0.09 g (0.591 mmol) of benzylisothiocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered,



wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)-N'-benzylthiocarbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES<sup>+</sup>)m/z = 995.

#### Example 31

##### **9-Deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)-N'-(1-naphtyl)thiocarbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A**

A mixture of 0.5 g (0.591 mmol) 9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A and 0.12 g (0.591 mmol) of 1-naphtylisothiocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)-N'-(1-naphtyl)thiocarbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES<sup>+</sup>)m/z = 1029.

#### Example 32

##### **9-Deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)-N'-(2-(trifluoromethyl)phenyl)carbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A**

A mixture of 0.5 g (0.591 mmol) 9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A and 0.08 g (0.591 mmol) of 2-(trifluoromethyl)phenylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-

-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)-N'-(2-(trifluoromethyl)phenyl)carbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES<sup>+</sup>)m/z = 1033.

### Example 33

#### **9-Deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)-N'-(3-phenylpropyl)carbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A**

A mixture of 0.5 g (0.591 mmol) 9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A and 0.10 g (0.591 mmol) of 3-phenylpropylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)-N'-(3-phenylpropyl)carbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES<sup>+</sup>)m/z = 1022.

### Example 34

#### **9-Deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)-N'-( $\beta$ -phenylethyl)thiocarbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A**

A mixture of 0.5 g (0.591 mmol) 9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A and 0.10 g (0.591 mmol) of  $\beta$ -phenylethylisothiocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)-N'-( $\beta$ -phenylethyl)thiocarbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES<sup>+</sup>)m/z = 1008.

**Example 35****9-Deoxo-9-dihydro-9a-N-[N'-(β-cyanoethyl)-N'-ethoxycarbonylmethylcarbamoyl]-γ-aminopropyl]-9a-aza-9a-homoerithromycin A**

A mixture of 0.5 g (0.591 mmol) 9-deoxo-9-dihydro-9a-N-[N'-(β-cyanoethyl)-γ-aminopropyl]-9a-aza-9a-homoerithromycin A and 0.10 g (0.591 mmol) of ethoxycarbonylmethylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-(β-cyanoethyl)-N'-ethoxycarbonylmethylcarbamoyl]-γ-aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES<sup>+</sup>)m/z = 974.

**Example 36****9-Deoxo-9-dihydro-9a-N-[N'-(β-cyanoethyl)-N'-[1-(1-naphtyl)ethyl]carbamoyl]-γ-aminopropyl]-9a-aza-9a-homoerithromycin A**

A mixture of 0.5 g (0.591 mmol) 9-deoxo-9-dihydro-9a-N-[N'-(β-cyanoethyl)-γ-aminopropyl]-9a-aza-9a-homoerithromycin A and 0.11 g (0.591 mmol) of 1-(1-naphtyl)ethylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-(β-cyanoethyl)-N'-[1-(1-naphtyl)ethyl]carbamoyl]-γ-aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES<sup>+</sup>)m/z = 1042.

**Example 37****9-Deoxo-9-dihydro-9a-N-[N'-(β-cyanoethyl)-N'-(3,4,5-trimethoxyphenyl)carbamoyl]-γ-aminopropyl]-9a-aza-9a-homoerithromycin A**

A mixture of 0.5 g (0.591 mmol) 9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A and 0.12 g (0.591 mmol) of 3,4,5-trimethoxyphenylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)-N'-(3,4,5-trimethoxyphenyl)carbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES<sup>+</sup>)m/z = 1053.

#### Example 38

##### **9-Deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)-N'-(2-naphtyl)carbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A**

A mixture of 0.5 g (0.591 mmol) 9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A and 0.11 g (0.591 mmol) of 2-naphtylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)-N'-(2-naphtyl)carbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES<sup>+</sup>)m/z = 1014.

#### Example 39

##### **9-Deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)-N'-(2,4-dichlorophenyl)carbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A**

A mixture of 0.5 g (0.591 mmol) 9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A and 0.11 g (0.591 mmol) of 2-naphtylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room

temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)-N'-(2,4-dichlorophenyl)carbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES<sup>+</sup>)m/z = 1033.

#### Example 40

##### **5-O-Desosaminy-9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)-N'-isopropylcarbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithronolide A**

A mixture of 0.5 g (0.728 mmol) 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-( $\gamma$ -aminopropyl)-9a-aza-homoerithronolide A and 0.06 g (0.728 mmol) of isopropylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)-N'-isopropylcarbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES<sup>+</sup>)m/z = 771.

#### Example 41

##### **5-O-Desosaminy-9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)-N'-(1-naphtyl)carbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithronolide A**

A mixture of 0.5 g (0.728 mmol) 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-( $\gamma$ -aminopropyl)-9a-aza-homoerithronolide A and 0.12 g (0.728 mmol) of 1-naphtylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered,

wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)-N'-(1-naphtyl)carbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES<sup>+</sup>)m/z = 855.

#### Example 42

##### **5-O-Desosaminy-9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)-N'-benzylcarbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithronolide A**

A mixture of 0.5 g (0.728 mmol) 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-( $\gamma$ -aminopropyl)-9a-aza-homoerithronolide A and 0.10 g (0.728 mmol) of benzylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)-N'-benzylcarbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES<sup>+</sup>)m/z = 819.

#### Example 43

##### **5-O-Desosaminy-9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)-N'-benzylthiocarbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithronolide A**

A mixture of 0.5 g (0.728 mmol) 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-( $\gamma$ -aminopropyl)-9a-aza-homoerithronolide A and 0.11 g (0.728 mmol) of benzylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)-N'-benzylthiocarbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES<sup>+</sup>)m/z = 835.

#### Example 44

**5-O-Desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(β-cyanoethyl)-N'-(1-naphtyl)thiocarbamoyl-γ-aminopropyl]-9a-aza-9a-homoerithronolide A**

A mixture of 0.5 g (0.728 mmol) 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-(γ-aminopropyl)-9a-aza-homoerithronolide A and 0.14 g (0.728 mmol) of 1-naphtylisothiocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(β-cyanoethyl)-N'-(1-naphtyl)thiocarbamoyl-γ-aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES<sup>+</sup>)m/z = 855.

#### Example 45

**5-O-Desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(β-cyanoethyl)-N'-(2-(trifluoromethyl)phenyl)carbamoyl-γ-aminopropyl]-9a-aza-9a-homoerithronolide A**

A mixture of 0.5 g (0.728 mmol) 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-(γ-aminopropyl)-9a-aza-homoerithronolide A and 0.14 g (0.728 mmol) of 2-(trifluoromethyl)phenylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(β-cyanoethyl)-N'-(2-(trifluoromethyl)phenyl)carbamoyl-γ-aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES<sup>+</sup>)m/z = 873.

**Example 46****5-O-Desosaminy-9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)-N'-(3-phenylpropyl)thiocarbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithronolide A**

A mixture of 0.5 g (0.728 mmol) 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-( $\gamma$ -aminopropyl)-9a-aza-homoerithronolide A and 0.13 g (0.728 mmol) of 3-phenylpropylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)-N'-(3-phenylpropyl)thiocarbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS( $\text{ES}^+$ ) $m/z$  = 863.

**Example 47****5-O-Desosaminy-9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)-N'-( $\beta$ -phenylethyl)thiocarbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithronolide A**

A mixture of 0.5 g (0.728 mmol) 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-( $\gamma$ -aminopropyl)-9a-aza-homoerithronolide A and 0.12 g (0.728 mmol) of  $\beta$ -phenylethylisothiocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)-N'-( $\beta$ -phenylethyl)thiocarbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS( $\text{ES}^+$ ) $m/z$  = .

**Example 48**



**5-O-Desosaminy-9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)-N'-ethoxy-carbonylmethylcarbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithronolide A**

A mixture of 0.5 g (0.728 mmol) 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-( $\gamma$ -aminopropyl)-9a-aza-homoerithronolide A and 0.09 g (0.728 mmol) of  $\beta$ -phenylethylisothiocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)-N'-ethoxycarbonylmethylcarbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES<sup>+</sup>)m/z = 815.

**Example 49**

**5-O-Desosaminy-9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)-N'-(2-naphtyl)carbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithronolide A**

A mixture of 0.5 g (0.728 mmol) 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-( $\gamma$ -aminopropyl)-9a-aza-homoerithronolide A and 0.12 g (0.728 mmol) of 2-naphtylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)-N'-(2-naphtyl)carbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES<sup>+</sup>)m/z = 855.

**Example 50**

**5-O-Desosaminy-9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)-N'-[1-(1-naphtyl)ethylcarbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithronolide A**

A mixture of 0.5 g (0.728 mmol) 5-O-desosaminyl-9-deoxo-9-dihydro-9a-N-( $\gamma$ -aminopropyl)-9a-aza-homoerithronolide A and 0.15 g (0.728 mmol) of 1-(1-naphthyl)ethylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)-N'-[1-(1-naphthyl)ethyl]carbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES<sup>+</sup>)m/z = 883.

#### Example 51

##### **5-O-Desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)-N'-(3,4,5-trimethoxyphenyl)carbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithronolide A**

A mixture of 0.5 g (0.728 mmol) 5-O-desosaminyl-9-deoxo-9-dihydro-9a-N-( $\gamma$ -aminopropyl)-9a-aza-homoerithronolide A and 0.14 g (0.728 mmol) of 3,4,5-trimethoxyphenylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)-N'-(3,4,5-trimethoxyphenyl)carbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES<sup>+</sup>)m/z = 895.

#### Example 52

##### **5-O-Desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)-N'-(2,4-dichlorophenyl)carbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithronolide A**

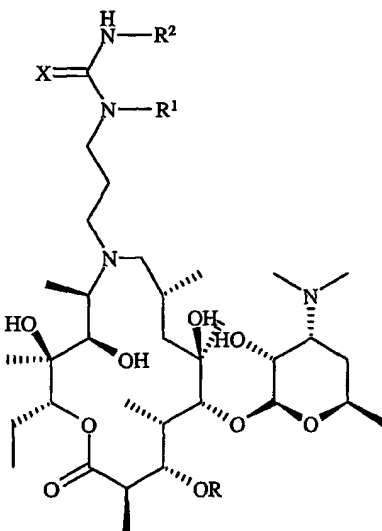
A mixture of 0.5 g (0.728 mmol) 5-O-desosaminyl-9-deoxo-9-dihydro-9a-N-( $\gamma$ -aminopropyl)-9a-aza-homoerithronolide A and 0.14 g (0.728 mmol) of 2,4-dichlorophenylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room

temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-[N'-( $\beta$ -cyanoethyl)-N'-(2,4-dichlorophenyl)carbamoyl- $\gamma$ -aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES<sup>+</sup>)m/z = 874.

## CLAIMS

1. N"-Substituted 9a-N-(N'-carbamoyl- $\gamma$ -aminopropyl), 9a-N-(N'-thiocarbamoyl- $\gamma$ -aminopropyl), 9a-N-[N'-( $\beta$ -cyanoethyl)-N'-carbamoyl- $\gamma$ -aminopropyl] and -9a-N-[N'-( $\beta$ -cyanoethyl)-N'-thiocarbamoyl- $\gamma$ -aminopropyl] derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminy-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A, novel semisynthetic macrolide antibiotics of the azalide series of the general formula 1,



1

- wherein R represents H or cladinosyl moiety, R<sup>1</sup> represents H or  $\beta$ -cyanoethyl moiety, R<sup>2</sup> represents isopropyl, 1-naphtyl, 2-naphtyl, benzyl, 2-(trifluoromethyl)phenyl, 3-phenylpropyl,  $\beta$ -phenylethyl, ethoxycarbonylmethyl, 1-(1-naphtyl)ethyl, 3,4,5-trimethoxyphenyl and 2,4-dichlorophenyl group, and X represents O and S, and their acceptable addition salts thereof with inorganic or organic acids.
2. Substance according to claim 1, characterized in that R represents cladinosyl group and R<sup>1</sup> represents H, R<sup>2</sup> represents isopropyl group and X is O.
  3. Substance according to claim 1, characterized in that R represents cladinosyl group, R<sup>1</sup> represents H and R<sup>2</sup> represents 1-naphtyl group and X is O.

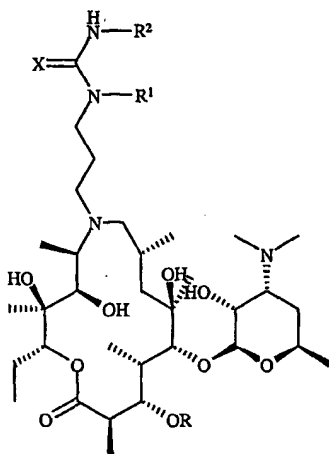
4. Substance according to claim 1, characterized in that R represents cladinosyl group, R<sup>1</sup> represents H and R<sup>2</sup> represents 2-naphtyl group and X is O.
5. Substance according to claim 1, characterized in that R represents cladinosyl group, R<sup>1</sup> represents H and R<sup>2</sup> represents benzyl group and X is O.
6. Substance according to claim 1, characterized in that R represents cladinosyl group, R<sup>1</sup> represents H and R<sup>2</sup> represents 2-(trifluoromethyl)phenyl group and X represents O.
7. Substance according to claim 1, characterized in that R represents cladinosyl group, R<sup>1</sup> represents H and R<sup>2</sup> represents 3-phenylpropyl group and X is S.
8. Substance according to claim 1, characterized in that R represents cladinosyl group, R<sup>1</sup> represents H and R<sup>2</sup> represents  $\beta$ -phenylethyl group and X is S.
9. Substance according to claim 1, characterized in that R represents cladinosyl group, R<sup>1</sup> represents H and R<sup>2</sup> represents etoxycarbonylmethyl group and X is O.
10. Substance according to claim 1, characterized in that R represents cladinosyl group, R<sup>1</sup> represents H and R<sup>2</sup> represents 1-(1-naphtyl)ethyl group and X is O.
11. Substance according to claim 1, characterized in that R represents cladinosyl group, R<sup>1</sup> represents H and R<sup>2</sup> represents 3,4,5-trimethoxyphenyl group and X is O.
12. Substance according to claim 1, characterized in that R represents cladinosyl group, R<sup>1</sup> represents H and R<sup>2</sup> represents 2,4-dichlorophenyl group and X is O.
13. Substance according to claim 1, characterized in that R represents cladinosyl group, R<sup>1</sup> represents H and R<sup>2</sup> represents benzyl group and X is S.
14. Substance according to claim 1, characterized in that R represents cladinosyl group, R<sup>1</sup> represents H and R<sup>2</sup> represents 1-naphtyl group and X is S.
15. Substance according to claim 1, characterized in that R represents cladinosyl group, R<sup>1</sup> represents  $\beta$ -cyanoethyl group, R<sup>2</sup> represents isopropyl group and X is O.
16. Substance according to claim 1, characterized in that R represents cladinosyl group, R<sup>1</sup> represents  $\beta$ -cyanoethyl group, R<sup>2</sup> represents 1-naphtyl group and X is O.

17. Substance according to claim 1, characterized in that R represents cladinosyl group, R<sup>1</sup> represents  $\beta$ -cyanoethyl group, R<sup>2</sup> represents 2-naphtyl group and X is O.
18. Substance according to claim 1, characterized in that R represents cladinosyl group, R<sup>1</sup> represents  $\beta$ -cyanoethyl group, R<sup>2</sup> represents benzyl group and X is O.
19. Substance according to claim 1, characterized in that R represents cladinosyl group, R<sup>1</sup> represents  $\beta$ -cyanoethyl group, R<sup>2</sup> represents 2-(trifluoromethyl)phenyl group and X is O.
20. Substance according to claim 1, characterized in that R represents cladinosyl group, R<sup>1</sup> represents  $\beta$ -cyanoethyl group, R<sup>2</sup> represents 3-phenylpropyl group and X is S.
21. Substance according to claim 1, characterized in that R represents cladinosyl group, R<sup>1</sup> represents  $\beta$ -cyanoethyl group, R<sup>2</sup> represents  $\beta$ -phenylethyl group and X is S.
22. Substance according to claim 1, characterized in that R represents cladinosyl group, R<sup>1</sup> represents  $\beta$ -cyanoethyl group, R<sup>2</sup> represents ethoxycarbonylmethyl group and X is O.
23. Substance according to claim 1, characterized in that R represents cladinosyl group, R<sup>1</sup> represents  $\beta$ -cyanoethyl group, R<sup>2</sup> represents 1-(1-naphtyl)ethyl group and X is O.
24. Substance according to claim 1, characterized in that R represents cladinosyl group, R<sup>1</sup> represents  $\beta$ -cyanoethyl group, R<sup>2</sup> represents 3,4,5-trimethoxyphenyl group and X is O.
25. Substance according to claim 1, characterized in that R represents cladinosyl group, R<sup>1</sup> represents  $\beta$ -cyanoethyl group, R<sup>2</sup> represents 2,4-dichlorophenyl group and X is O.
26. Substance according to claim 1, characterized in that R represents H, R<sup>1</sup> represents  $\beta$ -cyanoethyl group, R<sup>2</sup> represents benzyl group and X is S.
27. Substance according to claim 1, characterized in that R represents H, R<sup>1</sup> represents  $\beta$ -cyanoethyl group, R<sup>2</sup> represents 1-naphtyl group and X is S.

28. Substance according to claim 1, characterized in that R and R<sup>1</sup> represent H, R<sup>2</sup> represents isopropyl group and X is O.
29. Substance according to claim 1, characterized in that R and R<sup>1</sup> represent H, R<sup>2</sup> represents 1-naphtyl group and X is O.
30. Substance according to claim 1, characterized in that R and R<sup>1</sup> represent H, R<sup>2</sup> represents 2-naphtyl group and X is O.
31. Substance according to claim 1, characterized in that R and R<sup>1</sup> represent H, R<sup>2</sup> represents benzyl group and X is O.
32. Substance according to claim 1, characterized in that R and R<sup>1</sup> represent H, R<sup>2</sup> represents 2-(trifluoromethyl)phenyl group and X is O.
33. Substance according to claim 1, characterized in that R and R<sup>1</sup> represent H, R<sup>2</sup> represents 3-phenylpropyl group and X is S.
34. Substance according to claim 1, characterized in that R and R<sup>1</sup> represent H, R<sup>2</sup> represents β-phenylethyl group and X is S.
35. Substance according to claim 1, characterized in that R and R<sup>1</sup> represent H, R<sup>2</sup> represents ethoxycarbonylmethyl group and X is O.
36. Substance according to claim 1, characterized in that R and R<sup>1</sup> represent H, R<sup>2</sup> represents 1-(1-naphtyl)ethyl group and X is O.
37. Substance according to claim 1, characterized in that R and R<sup>1</sup> represent H, R<sup>2</sup> represents 3,4,5-trimethoxyphenyl group and X is O.
38. Substance according to claim 1, characterized in that R and R<sup>1</sup> represent H, R<sup>2</sup> represents 2,4-dichlorophenyl group and X is O.
39. Substance according to claim 1, characterized in that R and R<sup>1</sup> represent H, R<sup>2</sup> represents benzyl group and X is S.
40. Substance according to claim 1, characterized in that R and R<sup>1</sup> represent H, R<sup>2</sup> represents 1-naphtyl group and X is S.
41. Substance according to claim 1, characterized in that R represents H, R<sup>1</sup> represents β-cyanoethyl, R<sup>2</sup> represents isopropyl group and X is O.
42. Substance according to claim 1, characterized in that R represents H, R<sup>1</sup> represents β-cyanoethyl, R<sup>2</sup> represents 1-naphtyl group and X is O.
43. Substance according to claim 1, characterized in that R represents H, R<sup>1</sup> represents β-cyanoethyl, R<sup>2</sup> represents 2-naphtyl group and X is O.

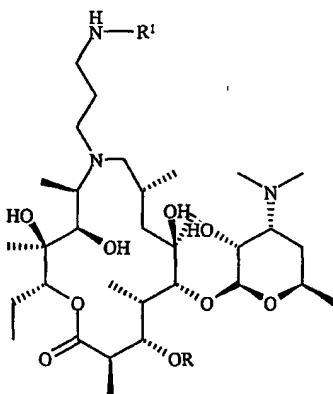
44. Substance according to claim 1, characterized in that R represents H, R<sup>1</sup> represents  $\beta$ -cyanoethyl, R<sup>2</sup> represents benzyl group and X is O.
45. Substance according to claim 1, characterized in that R represents H, R<sup>1</sup> represents  $\beta$ -cyanoethyl, R<sup>2</sup> represents 2-(trifluoromethyl)phenyl group and X is O.
46. Substance according to claim 1, characterized in that R represents H, R<sup>1</sup> represents  $\beta$ -cyanoethyl, R<sup>2</sup> represents 3-phenylpropyl group and X is S.
47. Substance according to claim 1, characterized in that R represents H, R<sup>1</sup> represents  $\beta$ -cyanoethyl, R<sup>2</sup> represents  $\beta$ -phenylethyl group and X is O.
48. Substance according to claim 1, characterized in that R represents H, R<sup>1</sup> represents  $\beta$ -cyanoethyl, R<sup>2</sup> represents ethoxycarbonylmethyl group and X is O.
49. Substance according to claim 1, characterized in that R represents H, R<sup>1</sup> represents  $\beta$ -cyanoethyl, R<sup>2</sup> represents 1-(1-naphtyl)ethyl group and X is O.
50. Substance according to claim 1, characterized in that R represents H, R<sup>1</sup> represents  $\beta$ -cyanoethyl, R<sup>2</sup> represents 3,4,5-trimethoxyphenyl group and X is O.
51. Substance according to claim 1, characterized in that R represents H, R<sup>1</sup> represents  $\beta$ -cyanoethyl, R<sup>2</sup> represents 2,4-dichlorophenyl group and X is O.
52. Substance according to claim 1, characterized in that R represents H, R<sup>1</sup> represents  $\beta$ -cyanoethyl, R<sup>2</sup> represents benzyl group and X is S.
53. Substance according to claim 1, characterized in that R represents H, R<sup>1</sup> represents  $\beta$ -cyanoethyl, R<sup>2</sup> represents 1-naphtyl group and X is S.
54. Process for the preparation of N''-substituted 9a-N-(N'-carbamoyl- $\gamma$ -aminopropyl), 9a-N-(N'-thiocarbamoyl- $\gamma$ -aminopropyl), 9a-N-[N'-( $\beta$ -cyanoethyl)-N'-carbamoyl- $\gamma$ -aminopropyl] and 9a-N-[N'-( $\beta$ -cyanoethyl)-N'-thiocarbamoyl- $\gamma$ -aminopropyl] derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminy-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A, of the general formula 1,





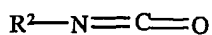
1

wherein R represents H or cladinosyl moiety,  $R^1$  represents H or  $\beta$ -cyanoethyl moiety,  $R^2$  represents isopropyl, 1-naphtyl, 2-naphtyl, benzyl, 2-(trifluoromethyl)phenyl, 3-phenylpropyl,  $\beta$ -phenylethyl, ethoxycarbonylmethyl, 1-(1-naphtyl)ethyl, 3,4,5-trimethoxyphenyl and 2,4-dichlorophenyl group, and X represents O and S, characterized in that 9a-N-( $\gamma$ -aminopropyl) and 9a-N-[N'-( $\beta$ -cyanoethyl)- $\gamma$ -aminopropyl] derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminy-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A general formula 2,



2

wherein R represents H and cladinosyl group and  $R^1$  represents H and  $\beta$ -cyanoethyl group is reacted with isocyanates or isothiocyanates general formula 3



3

wherein  $R^2$  represents isopropyl, 1-naphtyl, 2-naphtyl, benzyl, 2-(trifluoromethyl)phenyl, 3-phenylpropyl,  $\beta$ -phenylethyl, ethoxycarbonylmethyl, 1-(1-naphtyl)ethyl, 3,4,5-trimethoxyphenyl and 2,4-dichlorophenyl group, and X represents O and S, in toluene, xylene or some others aprotic solvents at a temperature 0°-110°C and then, if appropriate, to a reaction with inorganic or organic acids.

55. Pharmaceutical compositions comprising a pharmaceutically acceptable carrier and an antibacterially effective amount of the substances according to claim 1.
56. Use of a substance according to any claims 1 to 51 in the treatment of bacterial infections.

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(54) Title: NOVEL SEMISYNTHETIC MACROLIDE ANTIBIOTICS OF THE AZALIDE SERIES

(57) Abstract: The invention relates to N"-substituted 9a-N-(N'-carbamoyl-γ-aminopropyl), 9a-N-(N'-thiocarbamoyl-γ-amino-  
propyl), 9a-N-[N'-((β-cyanoethyl)-N'-carbamoyl-γ-aminopropyl)] and 9a-N-[N'-((β-cyanoethyl)-N'-thiocarbamoyl-γ-aminopropyl)]  
derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminy-9-deoxo-9-dihydro-9a-aza-9a-ho-  
moerithronolide A, novel semisynthetic macrolide antibiotics of the azalide series, of the general formula 1, wherein R represents  
H or cladinol moiety, R<sup>1</sup> represents H or (β-cyanoethyl) moiety, R<sup>2</sup> represents isopropyl, 1-naphtyl, 2-naphtyl, benzyl,  
2-(trifluoromethyl)phenyl, 3-phenylpropyl, β-phenylethyl, ethoxycarbonylmethyl, 1-(1-naphtyl)ethyl, 3,4,5-trimethoxyphenyl and  
2,4-dichlorophenyl group, and X represents O and S, and their acceptable addition salts thereof with inorganic or organic acids, to  
the process for preparation of their pharmaceutical compositions as well as the use their compositions in the treatment of bacterial  
infections.

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# INTERNATIONAL SEARCH REPORT

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## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07H17/00 A61K31/70 A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 492 688 A (BRIGHT GENE M) 8 January 1985 (1985-01-08) claim 9	1-56
A	WO 97/35590 A (PLATT CHRIS E) 2 October 1997 (1997-10-02) claim 4	1-56
A	EP 0 132 944 A (PFIZER) 13 February 1985 (1985-02-13) claim 1	1-56

☐ Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search

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Information on patent family members

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